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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/269, 673 07/16/99 HAYASHIZAKI

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EXAMINER

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ART UNIT	PAPER NUMBER
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1655

DATE MAILED:

10/19/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

<b>Office Action Summary</b>	Application No. <b>09/269,573</b>	Appl. Unit(s) <b>HAYASHIZAKI</b>
	Examiner <b>BJ Forman</b>	Group Art Unit <b>1655</b>

Responsive to communication(s) filed on 16 Jul 1999

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

Claim(s) 1-30 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

Claim(s) \_\_\_\_\_ is/are allowed.

Claim(s) 1-30 is/are rejected.

Claim(s) \_\_\_\_\_ is/are objected to.

Claims \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All  Some\*  None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

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## DETAILED ACTION

### *Specification*

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

2. Applicant is reminded that an English translation of a non-English-language application must be accompanied by a statement that the translation is accurate (see 37 CFR 1.52). A signed statement certifying the accuracy of the translation may be filed in with the response to this Office Action.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-30 are indefinite because “substance” is given more than one meaning. For example, Claim 1 & 9 which recite “substance specifically binding a mismatched base pair” and Claims 8, 18, 27 recite “labeled with at least one kind of substance”. It is suggested that the Claims be amended to define “substance” *i.e.* a protein or label

Claims 1-8 and 9-16 are indefinite because method claims must include steps that achieve the goal of the method. Specifically, a method for detecting a mutation must have a **mutation detection** step. It is suggested that the claims be rewritten to conform with current U.S. practice.

As an example, Claim 1 could be written as follows;

1. A method for detecting mutant nucleic acid and/or PNA fragments comprising the steps of:
  - a) hybridizing at least one fragment among one or more fragments fixed on a substrate, which fragments are selected from the group consisting of one or more nucleic acid fragments and/or one or more PNA fragments, with at least one fragment having a mutation to be assayed, wherein said fragment is selected from the group consisting of one or more nucleic acid fragments and/or one or more PNA fragments.
  - b) binding a labeled substance, which is a substance specifically binding to a mismatched base pair, to a mismatched base pair occurring between the hybridized fragments having a mutation.
  - c) identifying a fragment bound by the substance by detecting the label, thereby **detecting a nucleic acid and/or PNA fragments having a mutation**.

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Claim 6-8 lack proper antecedent basis because Claim 1 does not recite quantification. It is suggested that Claim 6 be amended to delete quantification or Claim 1 be amended to include a quantification step.

Claims 1, 9, 13, & 15 are indefinite because "substrate" is given two different meaning in the claims. Fragments are fixed on a "substrate" is recited in Claims 1 & 9 and labeled "substrate" is recited in Claims 13 & 15. It is suggested that Claims be amended to recite labeled fragment.

Claim 10 is a non sequitur to Claim 9 because it is not established that fragments are fixed at 5' ends *i.e.* the 3' ends are free. It is suggested that Claim 9 be amended to read, "fixed on a substrate at the 5' ends"(Claim 9, line 4).

Claim 15 lacks the proper antecedent basis for the limitation "substrate is labeled" because Claim 13 recites the fragments are labeled. It is suggested that the claim be amended to recite "fragment is labeled".

Claim 16-18 lack proper antecedent basis because Claim 9 does not recite quantification. It is suggested that Claim 16 be amended to delete quantification or Claim 9 be amended to include a quantification step.

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4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 23-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Gifford (U.S. Patent No. 5,750,335, 12 May 1998).

Claim 23 is drawn to a labeled substance which specifically binds a mismatched base pair. Gifford teaches labeled substances that specifically bind to mismatched base pairs (Column 5, lines 12-30).

Claim 24 is drawn to Claim 23 wherein the substance is a mismatch binding protein. Gifford teaches mismatch binding proteins that specifically bind to mismatched base pairs (Column 5, lines 12-30).

Claim 25 is drawn to Claim 24 wherein the protein is MutS, analogue thereof, or a C/C mismatch binding protein. Gifford teaches mismatch binding proteins *i.e.* MutS (Column 7, lines 14-42).

The limitations of Claims 23-25 are identical to the teachings of Gifford

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***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gifford as applied to claims 23-25 above, and further in view of Chee *et al.* (U.S. PATENT No. 5,837,832, 17 November 1998).

Claim 26 is drawn to Claim 23 wherein the label is GFP. Gifford does not teach the labeling of mismatch binding proteins with GFP. However, Gifford teaches labeling of the nucleic acids (Column 21, lines 1-18) and Chee *et al.* teach fluorescent labeling (Column 18, lines 57-68). Additionally, fluorescent labels, including GFP, were known in the art and routinely used in nucleic acid hybridization assays. The skilled practitioner, absent any unexpected results would have known to select GFP or any other label based on experimental requirements and/or expected results.

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6. Claims 1-8 & 19-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gifford (U.S. Patent No. 5,750,335, 12 May 1998) in view of Chirikjian et al. (U.S. Patent No. 5,763,178, 6 June 1998) and in further view of Chee, *et.al.* (U.S. PATENT No. 5,837,832, 17 November 1998).

Claim 1 of the instant applicant is drawn to a method for detecting a nucleic acid fragment and/or PNA fragment having a mutation comprising (A) hybridization of at least one fragment fixed on a substrate and one or more fragments wherein one or more fragments have a mutation; (B) binding a labeled substance which specifically recognizes mismatched base pairs; and (C) identifying a fragment bound by said substance of (B).

Gifford teaches a method for detecting and measuring mismatched base pairs which is essentially the same as that recited in the instant claims comprising (A) hybridization of a test nucleic acid with a reference nucleic acid; (B) binding a labeled mismatch binding protein to the nucleic acid hybrids; and (C) detecting the fragment with a mismatched base pair by detecting the labeled mismatch binding protein (Column 4 lines 10-67 & Column 5, lines 1-35). Claim 1 differs from Gifford in that Gifford does not teach fragments fixed on a substrate or the use of PNA fragments in the method. However, Chirikjian *et al.* do teach PNA fragments as DNA analogues in mismatch-detection hybridization assays. Specifically, Chirikjian *et.al.* teach the use of PNA (peptide nucleic acid) fragments as DNA probe analogues "for increased specificity in the detection of target nucleotides and point mutations therein" (Column 3, lines 8-14). In

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addition to the PNA teaching of Chirikjian *et.al.*, Chee *et al.* teach nucleic acid fragments fixed on a substrate and specifically teach the advantage of using fixed fragments is to “enhance detection of labeled targets” (i.e. MutS bound to fragments having a mismatched base pair ) (Column 7, lines 18-21).

Claim 2 is drawn to Claim 1 wherein the substance specifically binding to a mismatched base pair is a mismatch binding protein. Gifford teaches mismatch binding proteins that specifically bind to mismatched base pairs (Column 5, lines 12-30).

Claim 3 is drawn to Claim 2 wherein the mismatch binding protein is MutS, analogue thereof, or a c/c mismatch binding protein. Gifford teaches mismatch binding proteins *i.e.* MutS (Column 7, lines 14-42).

Claim 4 is drawn to Claim 1 wherein the substance specifically binding to a mismatched base pair is labeled. Gifford teaches labeled mismatch binding proteins (Column 5, lines 13-36).

Claim 5 is drawn to Claim 1 wherein the substance specifically binding to a mismatched base pair is labeled with GFP. Gifford does not teach the labeling of mismatch binding proteins with GFP. However, fluorescent labels, including GFP, were known in the art and routinely used in nucleic acid hybridization assays.

Claim 6 is drawn to Claim 1 wherein identification and quantification of the fragment having a mismatched base pair are performed by introducing a label into the fragment to be assayed and detecting the label to identify and quantify the mismatched base pair. Gifford

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teaches labeling of the nucleic acids to be assayed for identification and quantitation of the fragments (Column 21, lines 1-18).

Claim 7 is drawn to Claim 6 wherein the label introduced into the fragment produces a signal which is different from that produced by the label attached to the substance specifically binding to a mismatched base pair and quantification and identification of the fragment with a mismatched base pair are preformed simultaneously. Gifford teaches labeled test fragments and labeled mismatch binding proteins for simultaneous detection and quantitation (Claims 5 & 6).

Claim 8 is drawn to Claim 6 wherein the nucleic acid and/or PNA to be assayed for mutations is labeled with at least one kind of label selected from the group consisting of luminescent, fluorescent, phosphorescent substances, stable isotopes, radioactive substances, antibodies, antigens, enzymes and proteins. Gifford teaches labeling of the nucleic acids (Column 21, lines 1-18). Additionally, Chee *et al.* teach fluorescent labeling (Column 18, lines 57-68).

Claim 19 is drawn to Claim 1 wherein the fragments are fixed on the substrate only at the 3' or 5' end. Gifford does not teach fragments fixed on the substrate. However, Chee *et.al.* teach probes immobilized on a solid support as a way to screen a plurality of positionally distinguishable fragments for identification and quantification. Specifically, Chee *et.al.* teach 3' attachment of a nucleotide fragment to a substrate by (Claim 5).

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Claim 20 is drawn to Claim 1 wherein the fragments are fixed on the substrate by covalent bonds. Chee *et.al.* teach the 3' attachment of nucleotides to a solid surface with attachment via covalent linkage (Claim 5).

Claim 21 is drawn to Claim 1 wherein the fragments have a cDNA sequence. Gifford teaches that nucleic acid fragments may be cDNA (Column 4, lines 41-55).

Claim 22 is drawn to Claim 1 wherein the fragments have all or part of a cDNA sequence of a full length gene. Gifford teaches nucleic acid fragments may be any nucleotide sequence (*i.e.* cDNA) which encodes a protein (Column 4, lines 24-55).

Claim 27 is drawn to Claim 21 wherein the label is selected from the group consisting of luminescent, fluorescent, phosphorescent substances, stable isotopes, radioactive substances, antibodies, antigens, enzymes and proteins. Chee *et al.* teach fluorescent labeling (Column 18, lines 57-68).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the methods of Gifford and Chirikjian *et al.* for detecting base pair mismatches in nucleic acid (Gifford) and PNA (Chirikjian *et al.*) fragments and to further modify the method of Gifford for detecting base pair mismatches with the teachings of Chee *et al.* to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success to apply the method of

Gifford for detecting mismatch base pairs in nucleic acids to the closely related PNA as taught by Chirikjian *et al.* because the latter has “increased specificity in the detection of target nucleotides and point mutations” (Chirikjian *et al.*, column 3, line 8-11). Additionally, one of skill in the art would have been further motivated to apply the advantages of 3' covalent attachment of fragments to a substrate for hybridization as taught by Chee *et al.* to the method taught by Gifford for the expected benefit of “enhanced detection” as taught by Chee *et al.* (Column 7, line 19) in addition to the “increased specificity” as taught by Chirikjian *et al.* (Column 3, line 9)

7. Claims 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chirikjian *et al.* (U.S. Patent No. 5,763,178, 6 June 1998) in view of Chee, *et.al.*, (U.S. PATENT No. 5,837,832, 17 November 1998) and in further view of Goldrick (U.S. Patent No. 5,891,629, 6 April 1999).

Claim 9 is drawn to a method for detecting a nucleic acid and/or PNA fragment having a mutation comprising (A) hybridization of at least one fragment fixed on a substrate and one or more fragments wherein one or more fragments have a mutation; (D) binding a labeled substance which specifically recognizes and cleaves mismatched base pairs which removes at least a part of the fragment having the mismatched base pair; (E) labeling the fragment fixed to the substrate after cleavage; and (F) identifying the labeled fragment by detecting the label.

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Chirikjian *et al.* teach a method for detecting a nucleic acid and/or PNA fragment having a mutation which is essentially the same as that recited in the instant claims comprising; (A) hybridizing nucleic acid fragments (or PNA) wherein one or more fragments have a mutation to target nucleic acid fragments (or PNA) to form hybrids having a mismatch; (B) exposing the mismatched fragments to a base- repairing enzyme that cleaves the fragments having a mismatched binding pair; (C) detecting the cleaved hybrids (Column 14, lines 16-37). Chirikjian *et al.* does not teach fragments fixed on a substrate. However, Chee *et al.* teach nucleic acid fragments fixed on a substrate and specifically teach the advantage of using fixed fragments is to “enhance detection of labeled targets” (i.e. MutS bound to fragments having a mismatched base pair )(Column 7, lines 18-21).

Claim 10 is drawn to Claim 9 wherein 3' ends of the fixed fragments are blocked and labeling in step (E) is by a 3' end addition reaction. Chirikjian *et al.* teach addition of label to 3' end of cleaved fragment (Column 9, lines 32-38).

Claim 11 is drawn to Claim 9 wherein the substance specifically recognizing and cleaving the mismatched base pair is a nuclease. Chirikjian *et al.* teach base-repairing enzymes *i.e.* nuclease (Column 7, lines 16-34).

Claim 12 is drawn to Claim 11 wherein the nuclease is S1 nuclease, Mung bean nuclease, or RNASE H. Chirikjian *et al.* do not teach S1 nuclease, Mung bean nuclease, or RNase H but do teach other endonuclease. However, Goldrick teaches a method for detecting point mutations

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in nucleic acids using nuclease *i.e.* S1 nuclease, Mung bean nuclease and any or all of the RNases (Column 18, lines 61-64)

Claim 13 is drawn to Claim 9 wherein the labeling of the fragment in step (E) is by an enzyme reaction and labeled substrate. Chirikjian *et al.* teach addition of label to 3' end of cleaved fragment (Column 9, lines 32-38). Additionally, Chee *et al.* teach labeling by enzyme reaction and addition of labeled substrate (Column 22, lines 40-45).

Claim 14 is drawn to Claim 13 wherein the enzyme reaction is polymerase reaction, kinase reaction, ligation reaction, or 3' end addition reaction. Chee *et al.* teach DNA polymerase as an enzyme used in a labeling reaction (Column 22, line 44).

Claim 15 is drawn to Claim 13 wherein the label is selected from the group consisting of luminescent, fluorescent, phosphorescent substances, stable isotopes, radioactive substances, antibodies, antigens, enzymes and proteins. Chirikjian *et al.* teach radio labels. fluorescent labels, or "other labels" (Column 10, lines 1-5) and Chee *et al.* teach fluorescent labels (Column 22, lines 40-55)

Claim 16 is drawn to Claim 9 wherein detection and quantification of the fragment with a mismatched base pair are performed by introducing a label into the nucleic acid and/or PNA to be assayed for mutations and detecting the label. Chirikjian *et al.* teach detection and quantitation of the mismatched fragments (Column 9, lines 66-67 to Column 10, 1-13).

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Claim 17 is drawn to Claim 16 wherein the label produces a signal which is different from that produced by the label attached to the fragment in step (E) and quantification and identification are preformed simultaneously. Chirikjian *et al.* teach differential labeling to quantify and identify cleaved fragments (Column 10, lines 14-26).

Claim 18 is drawn to Claim 16 wherein the fragment labels are selected from the group consisting of luminescent, fluorescent, phosphorescent substances, stable isotopes, radioactive substances, antibodies, antigens, enzymes and proteins. Chirikjian *et al.* teach radio labels, fluorescent labels, or “other labels” (Column 10, lines 1-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Chirikjian *et al* with the teachings of Chee *et al.* to obtain the claimed invention because the skilled practitioner would have been motivated with a reasonable expectation of success to apply the hybridization method of detecting mutations in nucleic acid fragments to the substrate hybridization method of detecting mutations taught by Chee *et al.* for enhanced detection of target fragments as taught by Chee *et al.* Additionally, the skilled practitioner absent any unexpected results would have known to select fluorescent or any other labeling system based on experimental requirements and/or expected results.

8. Claims 28-30 are rejected as under 35 U.S.C. 103(a) as being unpatentable over Chee *et al.* in view of Chirikjian *et al.*

Claim 28 is drawn to a substrate having a surface on which one or more kinds of RNA or PNA fragments are fixed in a hybridizable condition. Chee *et al.* teach a substrate having a surface on which one or more DNA fragments or other nucleic acids fixed in a hybridizable condition (Column 5, lines 53-59). Chee *et al.* do not teach RNA or PNA fragments specifically. However, Chirikjian *et al.* do teach the use of PNA fragments as DNA analogues for “increased specificity in the detection of .....mutations” in hybridization assays (Column 3, lines 13-14). Absent unexpected results the nucleic acids fixed on a substrate could be DNA, or RNA as taught by Chee *et al.* or PNA as taught by Chirikjian *et al.* and it would have been known to one of skill in the art to select the nucleic acids based on experimental conditions or desired outcome.

Claim 29 is drawn to Claim 28 wherein the fragments are bound to the substrate only at the 3' or 5' ends. Chee *et.al.* teach the 3' attachment of nucleotides to a solid surface (Claim 5).

Claim 30 is drawn to Claim 28 wherein the fragments are fixed to the substrate by covalent bonds. Chee *et.al.* teach nucleotides on solid surface attached via covalent linkage (Claim 5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acids fixed on a substrate teaching of Chee *et al.* with the PNA teaching of Chirikjian *et al.* to obtain the claimed invention because the skilled practitioner would have been motivated with a reasonable expectation of success to use PANs as

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DNA analogues on substrates for hybridization assays because of the increased specificity of mutation detection as taught by Chirikjian *et al.*

9. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter that appears to be either identical with or only slightly different from process claimed. The methods for detecting a mutation in the instant application are disclosed in the prior art using either identical or only slightly different method steps. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (195 USPQ 430, second column, first full paragraph).

***REQUIREMENT FOR COMPLIANCE TO NUCLEIC ACID SEQUENCE RULES***

This application contains sequence disclosures (see page 16 of the specification) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With

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Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

***Conclusion***

10. No claim is allowed

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman, Ph.D. whose telephone number is (703) 306-5878. The examiner can normally be reached on Monday through Thursday and alternate Fridays from 7:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152. The official FAX phone number for this group is (703) 308-4242. The unofficial

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FAX number is (703) 308-8742. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.

October 18, 1999

*S. Forman*